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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	

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38

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/472,558	Applicant(s) BAHRAMIAN ET AL.	
	Examiner Peter Paras, Jr.	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,13-18,22-24,28-49,51 and 53-69* is/are pending in the application.

4a) Of the above claim(s) *28-49,51 and 53-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13-18,22-24 and 57-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/13/03 has been entered.

Claims 11 and 57 have been amended. New claims 68-69 have been added. Claim 25 has been cancelled. Claims 11, 13-18, 22-24, 28-49, 51, and 53-69 are pending. Claims 11, 13-18, 22-24, and 57-69 are under current consideration.

Election/Restrictions

Claims 28-49, 51 and 53-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5.

Sequence Compliance

The instant application is now in sequence compliance as Applicants have complied with 37 C.F.R. 1.821-1.825.

Drawings

The drawings received on 12/13/02 have been approved by the Draftsman and the Examiner.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 13-18, 22-24, and 57-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of muting expression of a α1(I) procollagen in cultured rodent fibroblasts, comprising introducing a plasmid containing a portion of the α1(I) procollagen nucleotide sequence identified as a muting nucleotide sequence, wherein the plasmid is transiently transfected into the rodent fibroblasts and the nucleotide sequence of endogenous α1(I) procollagen is not disrupted, wherein the α1(I) procollagen sequence is identified by screening nucleotide fragments of the endogenous gene to identify muting sequences, does not reasonably provide enablement for the claimed method comprising other embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The previous rejection is maintained for the reasons of record advanced on pages 4-8 (but not including the aspect of the rejection directed use of attenuated bacteria beginning on page 8) of the Office action mailed on 8/13/02.

Applicant's arguments filed 2/13/03 have been fully considered but they are not persuasive. Applicants assert that the specification provides guidance, which explains how one might screen for muting nucleic acids for genes other than procollagen (Example 15) and guidance that suggests that the muting effect is a general effect. Applicants go on to discuss that muting involves a coordinated transcriptional and post-transcriptional process, and point out that the 5' end of the gene is involved in the transcriptional mechanism and the 3' end of the gene is involved in the post-transcriptional mechanism. Applicants further discuss that there are transcriptional signals within intron I of the α1(I) procollagen gene, and assert that such is undoubted true with other genes, which could be the reason why the entire gene is important in muting as a general effect. Applicants point out that the coding sequences provide specificity for the active breakdown of cytoplasmic mRNA triggered by the post-transcriptional part of the dual mechanism. See page15-16 of the amendment.

In response, the Examiner asserts the evidence of record has not provided guidance for muting expression of endogenous genes other than α1(I) procollagen in cultured cells. The Examiner further asserts that no teaching provided by the evidence of record, which suggests whether the muting effect is general or specific; the mechanism of muting has not been disclosed. The Examiner maintains that a single working example directed to muting of a single gene, α1(I) procollagen gene, cannot be extrapolated to embrace muting of all genes as claimed. See pages 5-6 of the Office action mailed on 8/13/02. Moreover, Applicant's arguments appear to be off point for the following reasons: 1). The aspect of a coordinated transcriptional and post-

transcriptional process does not appear applicable to identifying of muting nucleic acid fragments and using identified fragments for muting as embraced by the claims; although it is not required it is noted that the claims do not specifically recite screening as a means of identifying. The instant specification (on page 26) discusses muting of endogenous procollagen mRNA by the combined 5' and 3' elements present in pWTC1, which could support the concept of a coordinated transcriptional and post-transcriptional process of muting since the specification has discussed that the 3' end of the procollagen gene contributes to post-transcriptional muting. It is noted that on page 13 of the specification it is discussed that pWTC1 contains the full-length procollagen gene. As such it appears that the full-length procollagen gene might be responsible for a coordinated transcriptional and post-transcriptional muting of the endogenous procollagen gene. Furthermore, the evidence of record does not support muting of endogenous procollagen by the 3' end of the gene alone; 2). The evidence of record has not provided a correlation between transcriptional signals within intron I of the procollagen gene and muting, particularly by a coordinated transcriptional and post-transcriptional process; and 3) The evidence of record has not provided specific coding nucleic acid sequences of procollagen that correlate to muting coding nucleic acid sequences of other genes. As such, the evidence of record has not provided support for the specificity of a particular sequence of nucleotides to muting, which correlates to all genes. Therefore, muting does not appear to be sequence-specific.

Applicants have argued that the likely mechanism of muting must occur via small dsRNA molecules, generated from the degradation of large heterogeneous anti-sense

RNA molecules, which have hybridized with mRNA from the endogenous gene, triggering its degradation. Applicants go on to assert that such a mechanism would be general to all cells. Applicants have pointed to Example 13 of the specification for support. See pages 17-18 of the amendment.

In response, the Examiner asserts that the evidence of record has not provided support for the mechanism of muting to occur through small dsRNA molecules. In fact Example 13, particularly in sentences 1-2 on page 30, teaches away from an anti-sense mediated mechanism for muting by stating "the gene muting of α1(I) was not mediated by synthesis of antisense RNA". Furthermore, Example 13 of the specification provides guidance for muting of the endogenous procollagen gene with the full-length procollagen gene contained within pWTC and does not encompass. It appears that the discussions on pages 26 and 30 of the specification provide evidence for a coordinated transcriptional and post-transcriptional process of muting the endogenous procollagen gene using the full-length procollagen gene contained within pWTC. However, the evidence has not provided a correlation between muting of endogenous procollagen with a full-length procollagen gene and muting of any other endogenous gene.

Applicants argue that the technology for producing RNA transcripts or DNA analogs is well known and does not need to be explained. See pages 18-19 of the amendment.

In response, the Examiner asserts that the evidence of record has only provided working examples where DNA sequences were used as muting sequences. It is maintained that the evidence of record has not provided guidance, which correlates

muting of an endogenous gene with delivery of a muting nucleic acid that is RNA or a DNA analog. See page 6 of the office action mailed on 8/13/02. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. In this case the conditions that would allow for muting expression of an endogenous gene using RNA or a DNA analog as the muting nucleic acid have not been disclosed.

Applicants have argued that the claims merely require identifying a muting sequence of double-stranded nucleic acid or a nucleic acid capable of becoming-double-stranded upon delivery, delivering the muting nucleic acid, and muting expression. Applicants further assert that there is no requirement that the muting sequence delivered is the actual molecule that affects muting in animal cells, rather that delivery of the muting sequence merely triggers muting by some other molecule in the cell. Applicants have contemplated that dsRNA is the likely candidate for muting. Applicants submit that claim 23 is readily understood as written. See pages 19-21 of the amendment.

In response, the Examiner asserts that Applicants are speculating as to the involvement of dsRNA in the mechanism of muting. But such reasoning appears off point as the specification does not support the involvement of dsRNA, particularly antisense RNA (See page 30 at the top) in muting. The evidence of record has not provided guidance that correlates the delivery of, for example, dsDNA, as the muting

nucleic acid, with involvement of dsRNA in the mechanism of muting, particularly because the claims require that muting is independent of integration, expression, or transcription of the delivered nucleic acid. It is maintained that the nature of the invention is unknown or otherwise undeveloped as no explanation of the mechanism of muting can be provided, which is supported by the evidence of record. Applicants have continued to argue that the skilled artisan can just make dsRNA or DNA analogs and deliver such to cells with expectation that muting will occur. It is maintained that the evidence of record has not provided guidance that correlates muting of endogenous genes with nucleic acid molecules other than dsDNA. See page 6-7 of the Office action mailed on 8/13/02.

Accordingly, the rejection is maintained for the reasons of record.

New Matter

Claims 11, 13-18, 22-24, and 57-62, and 65-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims embrace a method for muting expression of an endogenous gene in a population of animal cells, wherein the muting comprises muting at the level of post-transcription in the population as a whole.

The specification provides no implicit or explicit support for the context of the muting expression of an endogenous gene, other than α1(I) procollagen, in a population animal cells at the level of post-transcription. The specification has only provided support for muting at the post-transcriptional level in the context of muting the endogenous α1(I) procollagen gene (see page 23 lines 3-4 and p30 lines 15-18 as referenced by Applicants in support of the amendment to the claims), particularly when the muting nucleic acid comprises the 3' portion of the α1(I) procollagen gene (see page 14 lines 24-27). Patentees cannot pick characteristic possessed by two of their formulations and then make it basis of claims that cover any formulation having that characteristic. See Purdue Pharma L.P. v. Faulding Inc., 56 USPQ2D 1481 (CA FC 2000). Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or

terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure* [or point to case law supporting incorporation of such a limitation as in the instant case]" (emphasis added).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 13-18, 22-24, and 57-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 57, and 66-69 recite the limitation "muting nucleic acid " in step (b). There is insufficient antecedent basis for this limitation in the claim. Claims 13-18, 22-24 and 58-65 depend from claims 11 and 57 respectively.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The previous rejection of claims 11, 13-18, 22, 24, and 66 under 35 U.S.C. 102(b) as being anticipated by Guimaraes is withdrawn.

The previous rejection of claims 11, 13-18, 24-25, 57-62 and 65-67 under 35 U.S.C. 102(b) as being anticipated by Chan is withdrawn.

The previous rejection of claims 11, 13-18, 22, 24, 57-62 and 65-67 under 35 U.S.C. 102(b) as being anticipated by Rippe is withdrawn.

The previous rejection of claims 11, 13-17, 22-23, 57-61, 63-65 and 66-67 under 35 U.S.C. 102(b) as being anticipated by Slack is withdrawn.

The previous rejection of claims 11, 13-18, 22, 24, and 66 under 35 U.S.C. 102(b) as being anticipated by Gamborotta is withdrawn.

Conclusion

No claim is allowed. The claims appear to be free of the prior art but are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER